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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/640,989	08/14/2003	Lijun Yang	5853-261	9213

7590 12/22/2005

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EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 12/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/640,989	YANG, LIJUN	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8,9,12 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8,9,12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The reply received 11/14/05 amending claims 1, 8, 12, and 13 is acknowledged. Claims, 1, 8, 9, 12, and 13 are currently pending. The applicant should note that the examiner for this case changed upon the receipt of the reply to the restriction requirement.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Prior art references can be found in a prior Office action, unless otherwise noted.

Claim Objections

The objection to claim 1 is withdrawn in light of the claim amendments.

Claim Rejections - 35 USC § 112

Claims 8 and 9 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 9 were originally rejected because they recited a cell "wherein the cell is comprised in a liquid", which is confusing. The examiner suggested language such as "A composition comprising the cell of claim 1 and a liquid." Applicant has amended the claim to recite a cell that is "**cultured** in a liquid", which is confusing. It is not clear whether the limitation "cultured" is an active process step (in which case the claim is now drawn to a method) or a physical property. Clarification is required. In the interest of compact prosecution, the claim has been interpreted as being drawn to a composition comprising the cell of claim 1 and a liquid.

Claim Rejections - 35 USC § 102

Claims 1, 8, and 9 remain rejected under 35 U.S.C. 102(e) as being anticipated by Ramiya et al. (U.S. Patent Application Publication 2002/0182728). The claims are drawn to an insulin-producing cell isolated from an *in vitro* culture of human bone marrow cells. Some dependent claims have been interpreted as being drawn to a composition comprising said cells in a liquid, specifically tissue culture medium.

Ramiya et al. teach human bone marrow stem cells that express insulin after 45 days of growth in cell culture medium (paragraphs 0032 and 0059-0061; Figure 1).

Applicant alleges that Ramiya et al. do not teach or suggest that the cells of their invention actually produce any secreted insulin hormone (Remarks, page 8, paragraph 3). This argument has been fully considered, but it is not persuasive.

Applicant implies that "insulin-producing cells" necessarily produce insulin polypeptide and secrete it into the surrounding medium, but this definition is not supported either by the specification or by the art. The term "insulin-producing cells" has been interpreted in light of its plain meaning as referring to cells that produce the protein, whether it is secreted or not.

Applicant concurs that the cells of Ramiya et al. produce insulin mRNA, but implies that this mRNA is not necessarily translated into insulin polypeptide. Applicants cite paragraph 0059 of Ramiya et al., which describes RT-PCR/Southern blot analysis for the expression of various islet cell markers, including insulin mRNA. Applicants provide no evidence that the cells of Ramiya et al. were tested for the production of insulin polypeptide and found not to produce the polypeptide. Absent a substantive

evidentiary showing to the contrary, the person of ordinary skill in the art would infer from the expression of insulin mRNA that insulin polypeptide is produced. In fact, Ramiya et al. teach that the method described within the cited application produces insulin polypeptide (paragraph 0052). To overcome this rejection, applicant should provide substantive evidence that the cells of Ramiya et al. do not produce insulin polypeptide.

The above argument is merely the argument of counsel and is unsupported by evidence or declarations of those skilled in the art. Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See M.P.E.P. § 2129 and § 2144.03 for a discussion of admissions as prior art. Counsel's arguments cannot take the place of objective evidence. *In re Schulze*, 145 USPQ 716 (CCPA 1965); *In re Cole*, 140 USPQ 230 (CCPA 1964): and especially *In re Langer*, 183 USPQ 288 (CCPA 1974). See M.P.E.P. § 716.01(c) for examples of attorney statements that are not evidence and that must be supported by an appropriate affidavit or declaration.

Claims 1, 8, and 9 also remain rejected under 35 U.S.C. 102(e) as being anticipated by Black et al. (U.S. Patent Application Publication 2003/0104997). The claims are drawn to an insulin-producing cell isolated from an *in vitro* culture of human bone marrow cells. Some dependent claims have been interpreted as being drawn to a composition comprising said cells in a liquid, specifically tissue culture medium.

Black et al. teach human bone marrow cells that express insulin in cell culture medium (paragraphs 0057-0061, 0067, and 0102-0108).

Applicant alleges that Black et al. is non-enabling because the differentiation-inducing compound is not named (Remarks, page 9, paragraph 2). Applicant further alleges that Black et al. characterize marrow stromal cells as osteocytic, chondrocytic, and adipocytic precursors (*ibid.*). These arguments have been fully considered, but they are not persuasive.

Black et al. in fact disclose that the differentiation-inducing compound is 10 ng/mL basic fibroblast growth factor, bFGF, in serum-free DMEM and provide various protocols for the differentiation of mesenchymal stem cells to islet cells (paragraphs 0059, 0099, and 0103, for example). Therefore, absent a substantive evidentiary showing to the contrary, Black et al. is an enabling reference.

Applicant's assertion regarding Black et al.'s definition of marrow stromal cells is confusing. The instant claims are drawn merely to an insulin-producing cell isolated from an *in vitro* culture of bone marrow cells. The stromal cells of Black et al. are certainly bone marrow cells.

Claim Rejections - 35 USC § 103

Claims 1, 8, and 9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (1998, *Chinese Medical Journal English Edition* 111: 899-902) taken in view of Kuznetsov et al. (1997, *Journal of Bone and Mineral Research* 12:1335-1347). The claims are drawn to an insulin-producing cell isolated from an *in vitro* culture of human bone marrow cells. Some dependent claims have been interpreted as being drawn to a composition comprising said cells in a liquid, specifically tissue culture medium.

Wang et al. teach cultures of mouse Ltk- fibroblasts stably transfected with the human insulin gene; the clonal lines expressed high levels of insulin even after 6 weeks of culture (page 900, column 1, paragraph 2; page 900, column 2, paragraph 1; and Table). Wang et al. do not teach transfection of human bone marrow cells.

Kuznetsov et al. teach that human bone marrow comprises stromal fibroblasts (HMSFs; see Abstract and pages 2, 3, 6, and 7).

A person of ordinary skill in the art would have had a reasonable expectation of success in substituting the HMSFs of Kuznetsov et al. into the transfection protocol of Wang et al. because both cell lines are fibroblasts. The skilled artisan would have been motivated to make said substitution for the expected benefit that human cells are better suited for later transplantation into humans.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to transfect the HMSFs of Kuznetsov et al. with the human insulin gene construct of Wang et al. because Wang et al. teach that said construct can be transfected into and expressed by mammalian fibroblasts. The selection of fibroblast type and source clearly would have been a routine matter of optimization on the part of the artisan of ordinary skill, said artisan recognizing that Wang et al. teach that said construct can be transfected into and expressed by mammalian fibroblasts. A holding of obviousness over the cited claims is therefore clearly required.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicant alleges that Wang et al. do not teach "the isolation of a human bone marrow stem cell that produces insulin," but rather a cell into which an insulin gene has been transduced (Remarks, page 9, paragraph 6). Applicants further allege that the cited prior art teaches away from "an insulin producing cell that has **not** been transformed with a vector encoding an insulin gene" (emphasis in original), and the only way that a cell would produce insulin would be the introduction of the insulin gene into said cell (Remarks, page 10, paragraph 2). Applicants allege that neither reference teaches human bone marrow stem cells (*ibid.*). These arguments have been fully considered, but they are not persuasive.

Applicant's comments regarding the Wang et al. reference are noted, and the examiner agrees that Wang et al. teaches a population of fibroblasts into which an insulin gene has been transfected and that said fibroblasts would not produce insulin were they not transfected with a construct encoding functional insulin. The examiner points out, however, that the **claims** are not drawn to "a human bone marrow stem cell that produces insulin," but rather to **any** cell that has been obtained from an *in vitro* culture human bone marrow **and** produces insulin. As such, claim 1 encompasses cells isolated from human bone marrow that produce insulin as a direct result of the introduction of an exogenous functional insulin gene. The **claim** puts no limits on the nature of *in vitro* culturing encompassed by the limitation and, as such, reads on stable transfection, which is one type of *in vitro* culturing.

Similarly, the examiner agrees that neither Wang et al. nor Kuznetsov et al. teach "an insulin producing cell that has **not** been transformed with a vector encoding an

insulin gene," but points out again that the **claims** do not preclude that the cell be so transformed.

Applicant's comment that neither Wang et al. nor Kuznetsov et al. teaches human bone marrow stem cells is confusing, since Kuznetsov et al. clearly teaches human marrow stromal fibroblasts (see title and abstract, for example).

Claims 1, 8, 9, 12, and 13 remain rejected under 35 U.S.C. 103(a) as being unpatentable over either Ramiya et al. or Black et al. taken in view of Boyse et al. (U.S. Patent 5,004, 681), Polovina (U.S. Patent 5,580,714), and Gianni (U.S. Patent 5,649,904). The claims are drawn to an insulin-producing cell isolated from an *in vitro* culture of human bone marrow cells. Some dependent claims have been interpreted as being drawn to a composition comprising said cells in a liquid, specifically tissue culture medium. In some dependent claims, the cells are stored at a temperature below freezing, optionally in liquid nitrogen.

As discussed above, Ramiya et al. and Black et al. each teach a culture of human bone marrow cells that express insulin. Neither Ramiya et al. nor Black et al. teach freezing the cells.

Procedures for cryopreservation of mammalian cells in liquid nitrogen are known in the art. For example, Boyse et al. teaches that human bone marrow cells can be successfully recovered from long-term storage in liquid nitrogen (column 7, lines 1-4). Gianni teaches that techniques of bone marrow procurement, leukapheresis, and freezing are standard in the art (column 5, lines 36-39). Polovina teaches that stem cells

are capable of withstanding cryopreservation and thawing (column 4, lines 16-18) and provides one method for performing the same (column 8, lines 5-10).

A person of ordinary skill in the art would have had a reasonable expectation of success in cryopreserving the cells of Ramiya et al. or Black et al. in liquid nitrogen because Boyse et al. and Polovina teach that techniques for the same are well known and that bone marrow cells are not destroyed by freezing and thawing. The skilled artisan would have been motivated to cryopreserved the cells of Ramiya et al. or Black et al. for the expected benefit that the insulin-producing cells could be cultured on a large scale, then frozen in small aliquots for controlled thawing and use in downstream applications.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to cryopreserve the cells of Ramiya et al. or Black et al. because Boyse et al., Polovina, and Gianni teach that such a procedure is well known in the cell culture art.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicants rely in part on arguments traversing the rejections under section 102 to traverse this rejection (Remarks, page 10, paragraph 6). Therefore, the response set forth above to these arguments also applies to this rejection.

Applicants further allege that none of the cited references teach a composition in which "the cell would actually produce insulin after it has been frozen" (Remarks, page 11, paragraph 1). This argument has been fully considered, but it is not persuasive.

First, claims 12 and 13 merely require that the cell of claim 1 be stored at sub-freezing conditions, not that said cell produce insulin at said temperatures; surely, applicant does not mean to imply that the cells of the invention produce insulin at subzero temperatures.

The examiner suspects that applicant means to imply that the cells produce insulin after they have been frozen **and subsequently thawed** in accordance with art-accepted protocols. Even if this is the case, the argument is still not persuasive. As taught by Boyce et al., Gianni, and Polovina, cryopreservation and subsequent thawing was a routine practice in the eukaryotic cell culture art at the time of the invention and is known not to harm the cells or to interfere with their normal functions. Absent a substantive evidentiary showing that the cells of Ramiya et al. or Black et al. would lose their ability to produce insulin when subjected to the cryopreservation of Boyce et al., Gianni, and Polovina, the person of ordinary skill in the art would certainly have had a reasonable expectation of freezing said cells, thawing them, and observing insulin production.

Claims 1, 8, 9, 12, and 13 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. taken in view of Kuznetsov et al. as applied to claims 1, 8, and 9 above, and further in view of Boyse et al., Polovina, and Gianni. The claims are drawn to an insulin-producing cell isolated from an *in vitro* culture of human bone marrow cells. Some dependent claims have been interpreted as being drawn to a composition comprising said cells in a liquid, specifically tissue culture medium. In some

dependent claims, the cells are stored at a temperature below freezing, optionally in liquid nitrogen.

As discussed above, Wang et al. teach cultures of mouse Ltk- fibroblasts stably transfected with the human insulin gene; the clonal lines expressed high levels of insulin even after 6 weeks of culture. Wang et al. do not teach cryopreservation of human bone marrow cells.

Kuznetsov et al. teach that human bone marrow comprises stromal fibroblasts.

Procedures for cryopreservation of mammalian cells in liquid nitrogen are known in the art. For example, Boyse et al. teaches that human bone marrow cells can be successfully recovered from long-term storage in liquid nitrogen (column 7, lines 1-4). Gianni teaches that techniques of bone marrow procurement, leukapheresis, and freezing are standard in the art (column 5, lines 36-39). Polovina teaches that stem cells are capable of withstanding cryopreservation and thawing (column 4, lines 16-18) and provides one method for performing the same (column 8, lines 5-10).

A person of ordinary skill in the art would have had a reasonable expectation of success in cryopreserving the cells of Wang et al. taken in view of Kuznetsov et al. in liquid nitrogen because Boyse et al. and Polovina teach that techniques for the same are well known and that bone marrow cells are not destroyed by freezing and thawing. The skilled artisan would have been motivated to cryopreserved the cells of Ramiya et al. or Black et al. for the expected benefit that the insulin-producing cells could be cultured on a large scale, then frozen in small aliquots for controlled thawing and use in downstream applications.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to cryopreserve the cells of Wang et al. taken in view of Kuznetsov et al. because Boyse et al., Polovina, and Gianni teach that such a procedure is well known in the cell culture art.

Therefore, the invention as a whole would have been *prima facie* obvious to a person of ordinary skill at the time the invention was made.

Applicants rely in part on arguments traversing the rejection under section 103 over Wang et al. in view of Kuznetsov et al. to traverse this rejection (Remarks, page 11, paragraphs 4 and 5; and page 12, paragraph 1). Therefore, the response set forth above to these arguments also applies to this rejection.

Applicants further allege that Kuznetsov et al. teach osteogenic cells isolated from human foreskin, not cells isolated from human bone marrow (Remarks, page 11, paragraph 5). This argument has been fully considered, but it is not persuasive. The examiner agrees that Kuznetsov et al. teach human foreskin fibroblasts (page 4) but points out that Kuznetsov et al. clearly teach human stromal fibroblasts isolated from bone marrow (page 3, paragraph 2, through page 4, paragraph 1; page 6, paragraph 3).

No claims are allowed. No claims are free of the art.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Friday, 8:00am - 4:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SANDRA E. SAUCIER
PRIMARY EXAMINER

Lora E Barnhart

/LEB/